Neuroimmune Interaction in Inflammatory Diseases

Peyman Otmishi, Joshiah Gordon, Seraj El-Oshar, Huafeng Li, Juan Guardiola, Mohamed Saad, Mary Proctor and Jerry Yu

Pulmonary and Critical Care, Department of Medicine, Ambulatory Care Building, 3rd floor University of Louisville, Louisville, KY 40292, U.S.A.

Abstract: The inflammatory response is modulated through interactions among the nervous, endocrine, and immune systems. Intercommunication between immune cells and the autonomic nervous system is a growing area of interest. Spatial and temporal information about inflammatory processes is relayed to the central nervous system (CNS) where neuroimmune modulation serves to control the extent and intensity of the inflammation. Over the past few decades, research has revealed various routes by which the nervous system and the immune system communicate. The CNS regulates the immune system via hormonal and neuronal pathways, including the sympathetic and parasympathetic nerves. The immune system signals the CNS through cytokines that act both centrally and peripherally. This review aims to introduce the concept of neuroimmune interaction and discuss its potential clinical application, in an attempt to broaden the awareness of this rapidly evolving area and open up new avenues that may aid in the treatment of inflammatory diseases.

Keywords: vagus nerve, sensory nerve, inflammation, immune, autonomic nervous system

Neural Regulation of the Immune System

The CNS regulates the immune system through hormonal and neuronal pathways. The Hypothalamic-Pituitary-Adrenal (HPA) axis is the most important neuroendocrine pathway. Corticotropin releasing hormone (CRH) released from the paraventricular nucleus of the hypothalamus into the hypophyseal portal circulation causes the anterior pituitary gland to secrete adrenocorticotropin (ACTH). ACTH in turn induces the expression and release of glucocorticoids from the adrenal gland. Glucocorticoids suppress the immune system and have been used extensively in the treatment of inflammatory diseases since the 1940s (Webster, Tonelli, and Sternberg, 2002). In addition to affecting immune cell trafficking, migration, maturation and differentiation, glucocorticoids regulate the expression of cytokines, adhesion molecules, and chemotactic factors (Eskandari, Webster, and Sternberg, 2003). Glucocorticoids shift the cytokine pattern from pro-inflammatory [interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α)] to anti-inflammatory (IL-10) (Elenkov and Chrousos, 1999). Glucocorticoids act through a cytosolic glucocorticoid receptor that eventually translocates into the nucleus and binds to specific DNA sequences called glucocorticoid response elements to regulate gene transcription (Aranda and Pascual, 2001). Abnormalities in the signaling pathways can over-express or under-express certain inflammatory mediators, leading to diseases such as asthma (Leung et al. 1997), inflammatory bowel disease (Honda et al. 2000), and rheumatoid arthritis (Derijk et al. 2001). Other Hypothalamic-Pituitary-target axes, such as the Hypothalamic-Pituitary-Gonadal axis, have also been implicated in the immune response (Berczi, 2001). At physiological concentrations, estrogen enhances the immune response whereas androgens suppress it (Cutolo and Wilder, 2000). For this reason, autoimmune and inflammatory diseases are more common in females than in males (Olsen and Kovacs, 1996).

Dendritic cells are antigen presenting cells. Their bone marrow-derived precursors reach most tissue via the bloodstream, becoming resident immature dendritic cells. These cells mature after activation and initiate the immune responses toward foreign proteins (Caux, Liu, and Banchereau, 1995). After capturing antigens, dendritic cells migrate to the T cell-dependent lymphoid organs via the afferent lymph. Their migration depends on the cell maturation and on the concentration of neuropeptides released by the sensory neurons at the site of inflammation (Dunzendorfer et al. 2001).

Correspondence: Dr. Jerry Yu, Professor, Department of Medicine (Pulmonary), University of Louisville, Louisville, KY 40292, U.S.A. Tel: 502-852-5146; Fax: 502-852-1359; Email: j0yu0001@louisville.edu

Thus, stimulation of sensory nerve during inflammation may recruit antigen presenting cells to the inflammatory sites and therefore, propagate and control the degree of response.

Neural control of the immune system also occurs through the sympathetic and parasympathetic nerves. Both, in general, are anti-inflammatory. The sympathetic nerve innervates immune organs, such as the thymus, spleen and lymph nodes, causing effects through release of catecholamines. Immune cells (CD4+ T cells and B cells) express β_2 adrenergic receptors, supporting direct regulation by neurotransmitters released from sympathetic efferents (Kin and Sanders, 2006). Catecholamines decrease pro-inflammatory cytokines, stimulate anti-inflammatory cytokines, and favor a shift from Th1 (cellular) to Th2 (humoral) responses (Elenkov and Chrousos, 1999). The parasympathetic nerves innervate most visceral organs and regulate the immune response through the so called 'inflammatory reflex' by a vagal-vagal mechanism (Tracey, 2002). In this scenario, vagal afferents are stimulated by pro-inflammatory cytokines (TNF-α and IL-1β) and mediators (histamine and prostaglandins) and reflexively activate vagal efferents, via the solitary nucleus, to release acetylcholine (Ach) (Fig. 1). Subsequently, Ach acts through alpha-nicotinic receptors on macrophages to inhibit production of pro-inflammatory cytokines (Borovikova et al. 2000; Wang et al. 2003a). Stimulation of vagal afferents by intraperitoneal
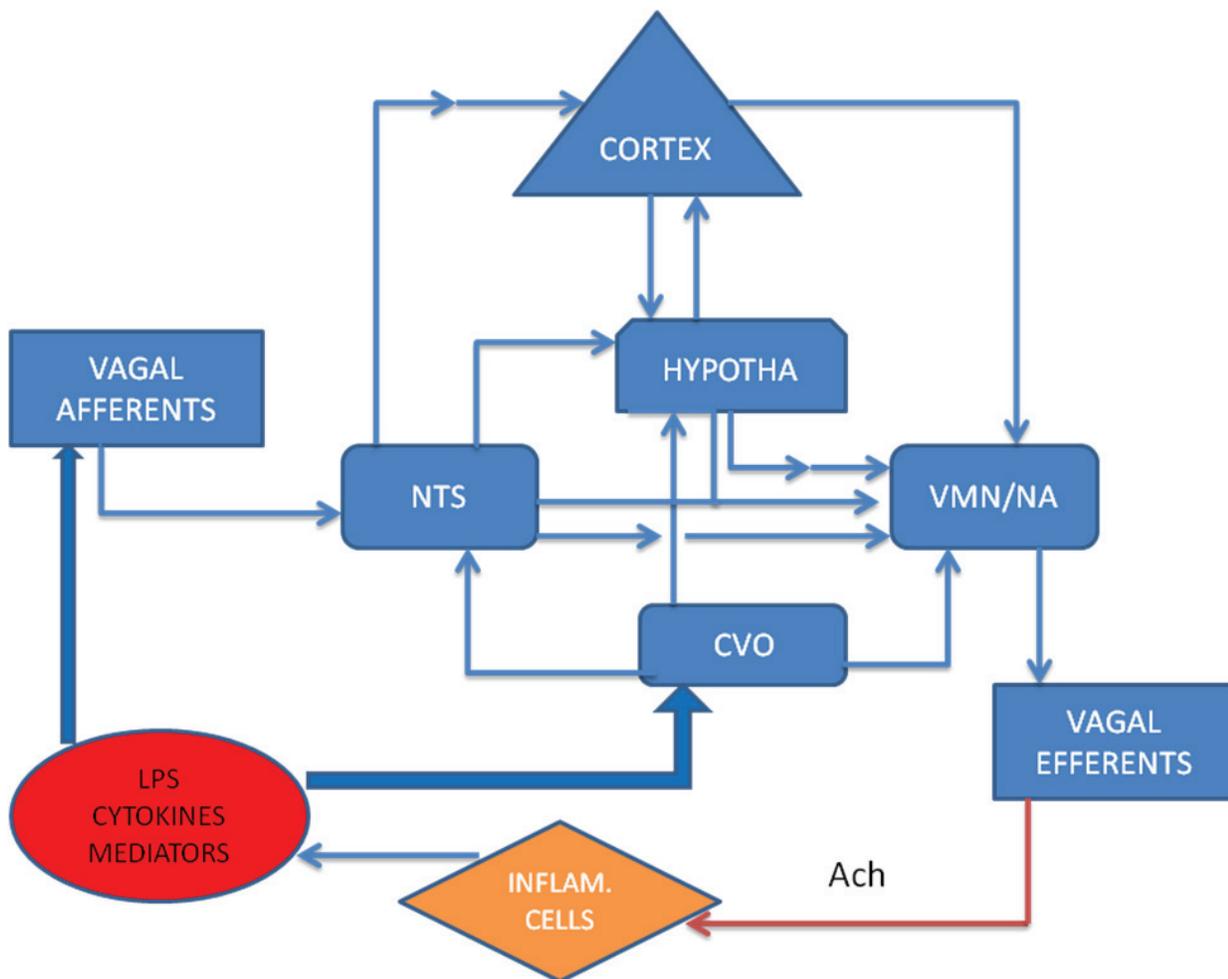

Figure 1. Illustration of a neuroimmune interaction. Inflammatory mediators and cytokines may activate vagal afferents, causing a 'reflex' via NTS to trigger neural circuitry and finally through vagal efferents to inhibit inflammatory cells to release inflammatory agents. The large, bold, blue arrows indicate initiation of the reflex pathway, while the thin, blue arrows denote a direct stimulatory effect; the red arrow indicates an inhibitory effect. Involvement of inter-neurons is indicated by two-arrow connections. LPS and high levels of cytokines and mediators may influence the higher brain centers via the CVO.

Abbreviations: Ach: Acytylcholine; CVO: Circumventricular Organ; Hypotha: hypothalamus; Inflam. cells: inflammatory cells; NA: Nucleus Ambiguous; NTS: Nucleus Tractus Solitarus; LPS: Lipopolysacharide; VMN: Vagal Motor Nucleus.

injection of IL-1β produces sickness responses (fever, lethargy, etc.), which is blocked by sub-diaphragmatic vagotomy (Goehler et al. 1999). Vagal afferent activity is also increased by exogenous IL-1β injected into the receptive field of vagal sensory afferents in the lung (Yu et al. 2007) or by abdominal injection of lipopolysaccharides (LPS) that increase endogenous IL-1β. Electrical stimulation of vagal afferents increases IL-1β expression in the brain and activates HPA axis (Hosoi, Okuma, and Nomura, 2000). Electrical stimulation of vagal efferents during lethal endotoxemia inhibits TNF synthesis in the liver and lowers its serum level, preventing endotoxemic shock (Borovikova et al. 2000). Furthermore, using nicotine to activate the cholinergic anti-inflammatory pathways reduces mortality of endotoxemia (Wang et al. 2004) and inhibits endothelial cell activation and leukocyte migration (Saeed et al. 2005). Vagotomy nearly doubled mortality in septic animals (Kessler et al. 2006). Moreover, the discovery that mast cells interact with the nervous system through synaptic cell adhesion molecules (Ito and Oonuma, 2006) has shed light into the complex neuron-immune reaction. This vast undiscovered area of physiology has sparked interest and coined the term "the neuro-immune system" of disease.

Influences of the Immune System on the CNS

The neuro-immune interaction is bidirectional through their soluble products: cytokines and mediators (Shepherd, Downing, and Miyan, 2005). Inflammatory cytokines play a crucial role in immune stimulation of nerves. Cytokines are a heterogenous group of polypeptides associated with activating the immune system and inflammatory responses. Cytokine receptors are found throughout the nervous system, including the CNS, vagus nerve, dorsal root ganglia, sciatic and sural nerves (Goehler et al. 1997; Plata-Salaman, 1991; Sorkin et al. 1997). IL-1β receptors are found even in carotid bodies (Wang et al. 2002). Activation of cytokine receptors contributes to neurological diseases such as multiple sclerosis, AIDS dementia complex, stroke, and Alzheimer's disease (Benveniste, 1998; Hopkins and Rothwell, 1995; Rothwell and Hopkins, 1995). During acute inflammatory states the immune response includes systemic release of

IL-1, which acts on the brain to activate the HPA axis to modulate the inflammatory response (Haddad, Saade, and Safieh-Garabedian, 2002).

Cytokines exert their effects on the CNS by various mechanisms, including: 1) by crossing the blood brain barrier through an active transport mechanism, 2) by passively diffusing through brain areas called circumventricular organs (CVO), where the fenestrated capillaries allow for higher permeability. Through the CVO, the brain can monitor levels of cytokines and mediators in the blood, and 3) by directly activating peripheral sensory nerves (Hosoi, Okuma, and Nomura, 2002). Pro-inflammatory cytokines or mediators may induce a series of mood and behavioral changes (collectively termed sickness behaviour, which is adaptive and helps the host to prevent system failure) by acting on receptors in the CNS, which are identical to those found on immune cells (Dantzer, 2004). The vagus nerve innervates a vast majority of internal organs, hence it can potentially receive various immune stimuli and convey immunological information to the CNS (Goehler et al. 1997; Watkins et al. 1995). In addition, fever develops within minutes following the peripheral injection of LPS when concentrations are not adequate to affect the brain in time to account for the response (Hosoi, Okuma, and Nomura, 2002; Kluger, 1991). These observations support a neural pathway that conveys peripheral immune signals to the brain and suggest a surveillance role of the CNS in numerous systemic diseases related to organ dysfunction like Irritable Bowel Syndrome and Acute Lung Injury.

In summary, the nervous system regulates the immune responses. Inflammation, a common mechanism involved in the pathophysiological process of various diseases, is an integral part of innate immune responses. Inflammatory products activate sensory nerves and send signals regarding the state of the inflammation to the CNS. Furthermore, through the reflex, efferent nerves can release mediators that act on immune cells (Fig. 1). In the following sections, we will discuss some particular inflammatory diseases associated with neuroimmune interaction.

Rheumatology

Rheumatoid arthritis (RA) affects 1% of the general population, making it the most common form

of chronic inflammatory arthritis. RA can be divided into two main phases: pre-clinical and clinical. The pre-clinical phase is asymptomatic (Vassilopoulos and Mantzoukis, 2006), when auto-antibodies can be detected in blood (Nielen et al. 2004). Neuronendocrine interaction plays a crucial role at this stage. The clinical phase is symptomatic and can be further divided into early and chronic phases. Chronic inflammation alters neuropeptide processing, leading to long-term functional and structural changes in innervation, neurovascular regulation, and immune modulation. An altered HPA axis in RA points to an interaction between the disease and the neuroendocrine system.

The symmetric involvement of joints in RA and autonomic dysfunction associated with RA provides a compelling link of the disease with the CNS. Additionally, patients with central or peripheral hemiparesis who later develop RA, do not have joint disease in the paretic limbs, further suggesting neuronal involvement. In Sprague Dawley rats, inflammation (swelling and hyperalgesia) induced in one hindpaw produced the same signs in the contralateral paw with a similar magnitude and duration (Levine et al. 1985b). Chronic denervation of either the injured or the uninjured limb markedly attenuated the contralateral inflammatory response. This suggests that local inflammation can stimulate sensory nerves and reflexively produce inflammatory responses in the contralateral limb. In addition, denervation by capsaicin in either hind limb attenuates the contralateral responses, indicating an involvement of afferent C-fibers. Vein ligation has no effect on the inflammatory responses observed, excluding the possibility of humoral mediation (Levine et al. 1985a).

In physiological states, synovial nociceptors (C fibers and $A\delta$ fibers) remain silent. During inflammation, however, they become sensitized to chemical, mechanical and thermal stimulation via two mechanisms. First, the mechanosensitive myelinated A fibers mediate sensitization at the pre-synaptic (CNS) level through repeated, prolonged stimulation. Second, soluble cytokines and inflammatory mediators (prostaglandins, adenosine, serotonin, and bradykinin) can directly sensitize neurons, including nociceptors (Niissalo et al. 2002). TNF-α and IL-1β play vital roles in joint inflammation and bone destruction. Immun-modulators such as steroids, anti-TNF, and anti-IL-1 have become the mainstay treatment in severe RA. The immune response is predominantly regional, but can be systemic. Substance-P (SP) released by sensory fibers in the inflamed synovium, cytokines such as TNF-α and IL-2, and circulating activated immune cells have all been implicated in rheumatoid pathology (Straub and Cutolo, 2001). For example, SP, which is pro-inflammatory, is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes and dendritic cells and acts through its neurokinin-1 (NK-1) receptor. SP and NK-1 receptor mRNA levels are elevated in the synovium and synoviocytes of patients with RA. Joint inflammation involves plasma extravasation, infiltration of the synovium with inflammatory cells, followed by vascular remodeling. SP potentiates plasma extravasation and enhances inflammatory responses in a mouse arthritis model (Keeble et al. 2005). Inflammatory signals activate the HPA axis and the hypothalamic-autonomic nervous system axis, exerting anti-inflammatory effects in arthritic joints through cortisol and catecholamines. In theory, an inadequate neuroendocrine response may result in the transition from the early to chronic phase in RA. Sympathetic responses are increased in RA patients following stimulation of sensory fibers in synovial tissue. Despite this, the number of sympathetic fibers in inflamed RA joints is lower than in non-inflammatory joints (Miller et al. 2000). Perhaps this loss of sympathetic fibers prevents the host from conveying anti-inflammatory actions through the sympathetic system.

Following exposure to streptococcal cell wall antigen, chronic arthritis develops in Lewis rats, which have a blunted HPA response, but not in Fischer rats having an increased hypothalamic CRH response. Glucocorticoid antagonists increase the susceptibility to arthritis, while glucocorticoids suppress the inflammatory response in arthritic rats (Vassilopoulos and Mantzoukis, 2006). However, arthritis in rat models is a polygenic disease where the impact of genetic variability on phenotypic expression accounts for about one-third of the cases. In human RA, genetic analysis for disease susceptibility has been performed around the world. Human Leukocyte Antigen (HLA)-related genes may be involved in predisposition to disease in about one-third of the cases, whereas non-HLA regions are responsible for remainders (Steinsson and arcon-Riquelme, 2005). Newly developed gene

identification techniques may help determine if genes associated with the neuroendocrine axis play a role in RA predisposition.

The neuroendocrine link has also been implicated in Sjogren's syndrome (Johnson and Moutsopoulos, 2000), chronic fatigue syndrome and fibromyalgia (Moldofsky, 1995). Sjogren's syndrome is a perfect model for studying alterations in the neuroendocrine-immune system, since patients are usually medication free and hence devoid of the confounding effects of immunosuppressive treatment (Johnson and Moutsopoulos, 2000).

Neurological Diseases

There has been much interest in the relationship between inflammation and pain. Painful information (nociception) is relayed to the CNS through afferent nerves, which are mostly comprised of unmyelinated C fibers and myelinated Aδ fibers. These afferents synapse to second order neurons in the dorsal horn of the spinal cord. Nociceptors are usually polymodal, responding to a variety of noxious stimuli (Kidd and Urban, 2001). Tissue inflammation or injury generates a surge of inflammatory mediators (cations, bradykinin, histamine, 5 HT, ATP, nitric oxide and cytokines). These mediators can either directly stimulate or sensitize the nociceptors. They can also increase production and release of more inflammatory mediators, leading to nociceptor activation. Hence, pro-inflammatory mediators may play a major role in the pathogenesis of chronic neuropathic pain syndromes.

Painful neuropathies are caused by nerve injury from inflammatory disease or trauma, and are influenced by cytokines and immune mediators (Baron, 2000). Their study can be traced back to Mitchell's classic work from the American Civil War (Moalem and Tracey, 2006). Nerve injury activates resident immune cells and recruits inflammatory cells to the injured sites, initiating an inflammatory cascade. Mast cells near the nerve are activated to release histamine and TNF-α, which recruit neutrophils and macrophages, as well as sensitize nociceptors. In turn, the recruited inflammatory cells secrete cytokines and mediators (TNF-α and PGE$_2$) that can further sensitize nociceptors. Nerve injury releases mediators, including ATP, nerve growth factor, PGE$_2$ and pro-inflammatory cytokines. This promotes recruitment of T cells, secreting a variety of cytokines. This cocktail of mediators enhances the inflammation and contributes to pain (Moalem and Tracey, 2006). Focal neuritis in the rat sciatic nerve produces neuropathic pain sensations. Neuroimmune interaction occurs at the outset of nerve injury that produces neuropathic pain. For example, TNF-α can be released from sciatic Schwann cells (Wagner and Myers, 1996) and injection of TNF-α and IL-1β into rat sciatic nerve causes pain (Zelenka, Schafers, and Sommer, 2005). TNF-α can stimulate the sciatic nerve directly. Intradermal injection of TNF-α leads to sensitization and subsequent hyperalgesia (Sorkin et al. 1997). Such an interaction may prime the system for slowly developing sustained pain during the chronic phase of neuropathy (Bennett, 1999). Over time, episodic priming, by the release of inflammatory mediators, may also contribute to chronic conditions like diabetic neuropathy. Guillain-Barré Syndrome, an autoimmune injury of the peripheral nervous system causing demyelination, is characterized by progressive ascending polyneuropathy, which may progress to quadriplegia and lead to respiratory arrest. A strong correlation of serum levels of TNF-α and its receptors with disease severity and recovery is found in patients with Guillain-Barré Syndrome (Radhakrishnan et al. 2003).

Sympathetic nerve has been investigated in various studies related to neuroimmune interaction, including the pathogenesis of multiple sclerosis (Elenkov et al. 2000). Receptors for sympathetic neural transmitter, $\beta2$ adrenoceptors, provide important protective and supportive functions in cell proliferation, response, and metabolism. Astrocytes in multiple sclerosis lack $\beta2$ adrenoceptors (De et al. 2004), the activation of which inhibits the expression of pro-inflammatory cytokines via cAMP. Lack of $\beta2$ adrenoceptors may also transform astrocytes into facultative antigen presenting cells, initiating the inflammatory cascade. $\beta2$ receptor defects also impair glycogenolysis, which generates lactate as an energy source for axons. Disturbances in axonal metabolism may cause accumulation of calcium ions inside the axon and thus degeneration. This rationale might provide a new therapeutic strategy to reduce or prevent both relapses and the progression of multiple sclerosis by increasing c-AMP levels in astrocytes (De et al. 2004).

Gastrointestinal Tract

Recent research demonstrates the interrelationship between the nervous system and the

mucosal immune system (Shanahan, 1999). In the gastrointestinal (GI) tract, activated mast cells release inflammatory mediators, which in turn stimulate sensory nerve endings (De Jonge et al. 2005). Activation of sensory nerves initiates 'the inflammatory reflex', releasing acetylcholine from vagal efferents and inhibiting cytokine production by macrophages (De Jonge et al. 2005). Furthermore, vagotomy leads to increase levels of IL-6, TNF-α and IL-1β in the gut (Ghia et al. 2006), exemplifying the vagal anti-inflammatory effects. Such a mechanism explains a well-established relationship between tobacco use (nicotine) and inflammatory bowel disease (IBD). In ulcerative colitis, the protective effect of nicotine is related to the α7-subunit and its inhibition of TNF-α (Johnson, Cosnes, and Mansfield, 2005) and IL-8 (Louvet et al. 1999). Bowel manipulation, transplantation, and ischemia/reperfusion injury activate intestinal macrophages and cause acute gut inflammation. The pathogenesis of post-operative ileus exemplifies such a mechanism. Macrophages are activated in the muscularis externa of the human small bowel following intestinal manipulation (Kalff et al. 2003). Once activated, these resident macrophages release pro-inflammatory mediators that cause bowel inflammation and inhibit contractility. Local inflammation can also inhibit distant sites, demonstrating that a neural pathway can paralyze the entire GI tract (de Jonge et al. 2003).

Inflammatory bowel disease, including Crohn's disease and ulcerative colitis, is characterized by overproduction of inflammatory cytokines, dysregulation of mucosal immunity and uncontrolled inflammation in the gut. In patients with IBD, structural abnormalities include enteric glial cell hyperplasia (Geboes and Collins, 1998), ganglion cell and axonal degeneration, and necrosis (Dvorak et al. 1993). Functionally, enteric glial cells are equivalent to astrocytes in the CNS (Cabarrocas, Savidge, and Liblau, 2003). Enteric glial cells and neurons in Crohn's Disease express a major histocompatibility complex class 2 antigen on their cell surface (similar to macrophages) allowing them to act as antigen presenting cells and release pro-inflammatory cytokines and mediators (Geboes et al. 1992). SP has been implicated in IBD pathology. In IBD mouse models, NK-1 receptors (the binding sites for SP) were up-regulated in intestinal tissue. NK-1 receptor antagonists decreased disease severity and promoted healing pre-existing lesions (Sonea et al. 2002). Infliximab, an antibody, which neutralizes TNF-α and down-regulates interferon gamma production (Agnholt and Kaltoft, 2001), benefits patients with active steroid-dependent or with fistulizing Crohn's disease. All stated above are consistent with that neuroimmune interactions play a role in the pathogenesis of IBD. Perhaps new avenues will open up for designing drugs to modify the disease course and decrease the morbidity of IBD.

Irritable bowel syndrome (IBS) is the consequence of altered visceral perception and regulation of gastrointestinal motility and epithelial function, and is associated with CNS disturbance and psycosocial stresses (Barbara et al. 2004). The syndrome may accrue from primary alterations in the periphery or in the CNS, or a combination (Mayer, Naliboff, and Chang, 2001). Brain-gut interactions are mediated by outputs from the autonomic and neuroendocrine systems, as well as from attentional and pain modulatory responses. Psychological and physical stressors affect function of the GI tract through neuronal activity within emotion-specific circuits in the brain, and therefore enhancing gastric motility, mucosal blood flow and acid secretion. In response to internal or external stress, pro-inflammatory cytokines in the GI tract are increased. This causes perception of symptoms via intrinsic and extrinsic primary afferent neurons (Barbara et al. 2004), which in turn further activates the neuronal circuits, intensifying the symptoms. Thus, IBS patients have an enhanced GI responsiveness due to malfunction of the neuroendocrine-immune interaction (Mulak and Bonaz, 2004). In the last 20 years, low dose antidepressants have been successfully used to treat IBS patients, partly due to their neuromodulator properties, in addition to their analgesic effects (Wald, 2002).

Lastly, neuroimmune interaction may also account for some cases of appendicitis that are negative for inflammation on histopathology. These are associated with neuroproliferation and increased SP and vasointestinal polypeptides. This distinct pathological entity, neuroimmune appendicitis, explains up to 25% of normal appendixes in surgical patients (Di et al. 1999). In experimental pancreatitis, the vagus nerve provides a

protective function through anti-inflammatory effects via nicotinic receptors (van Westerloo et al. 2006). This may result in new approaches to treating acute pancreatitis besides bowel rest and pain analgesia.

Respiratory System

Pulmonary nociceptors, the most abundant afferent nerves in the lung, are sensitive to inflammatory products, such as histamine, prostaglandins, and SP (Coleridge and Coleridge, 1984; Lee and Pisarri, 2001). Rodent nociceptors are associated with neuropeptides, SP, tachykinins, and Calcitonin Gene-Related Peptide, as well as other neurokinins. These neuropeptides are responsible for neurogenic inflammation through the interaction of nociceptive fibers and alveolar macrophages, releasing neuropeptides and cytokines, respectively (McDonald, 1987; Solway and Leff, 1991). TNF-α increases bronchial tissue responsiveness (Anticevich et al. 1995), suggesting a role of inflammatory cytokines in asthma and COPD. Accumulating evidence indicates the neuroendocrine and immune systems interact during the development of asthma (Marshall, Jr. and Agarwal, 2000). Many mediators released in the inflammatory zone may modulate sensory and motor nerves in the airways (Barnes, 1992). Sensory nerves, in turn, may amplify inflammation through the release of peptide neurotransmitters. Electrical stimulation of the cervical vagus nerve evokes neurogenic inflammation in the trachea and bronchi of rats. Neural mediators modulate the pulmonary inflammatory response by triggering vasodilatation, tissue edema, and influx of inflammatory cells (Kraneveld and Nijkamp, 2001). SP and neurokinin are involved in bronchoconstriction and mucous production. The presence of SP in sensory fibers is the groundwork of neurogenic inflammation. Interestingly, mechanosensors in the lung, which do not express SP, become SP immune reactive after allergen challenge in guinea pigs. Ipsilateral vagotomy suppresses the SP expression (Chuaychoo et al. 2005). Nerve growth factor, which is closely associated with asthma, is released from lung fibroblasts at an increased rate when exposed to TNF-α and IL-1β (Olgart and Frossard, 2001). Pulmonary afferents, traveling through sympathetic nerves, also exist (Soukhova et al. 2003; Wang et al. 2003b) and potentially contribute to lung pathophysiology. Acute hypoxia influences the neuroimmune system through the action of IL-1β under numerous conditions (asthma, chronic obstructive lung disease, sleep apnea and heart failure) (Johnson et al. 2007). In addition, emotions have a clear influence on asthmatic attack. A number of studies have found a relationship between asthma and negative emotions, such as anxiety, anger, and sadness (von, Ehnes, and Dahme, 2006), supporting a neuroimmune interaction.

Acute Respiratory Distress Syndrome (ARDS) is a major source of intensive care mortality because of its association with other acute disorders (infection, trauma, sepsis, intoxication, or pancreatitis). Pro-inflammatory cytokines may be crucial in the initiation, propagation, maintenance and regression of the inflammatory response in the lungs by stimulating pulmonary nociceptors. Pro-inflammatory cytokines are markedly elevated in broncho-alveolar lavage (BAL) samples from patients with ARDS, or those at risk for ARDS (Siler et al. 1989; Suter et al. 1992). TNFα, IL-1β and IL- 6 in plasma and BAL are increased in non-survivors of ARDS (Meduri et al. 1995). Furthermore, pulmonary nociceptor activity is increased dramatically during oleic acid-induced ARDS (Lin et al. 2007) or by direct injection of the inflammatory cytokine IL-1β into the sensory receptive field (Yu et al. 2007). This supports neuroimmune interaction mechanisms during acute pulmonary events.

Conclusion

As a mechanism, neuroimmune interaction controls inflammation in multiple diseases. The connection between the brain and inflammatory diseases is not restricted to the previous examples. Brain-skin interaction is increasingly recognized. For example, atopic dermatitis patients demonstrate a blunted HPA axis response (Buske-Kirschbaum et al. 2002). Neurokinins derived from sensory nerves interact with antigen presentation in dermal Langerhans cells in allergic skin disease (Darsow and Ring, 2001). Intracerebral administration of melanocyte-stimulating hormone α can inhibit cytokine-induced cutaneous inflammation (Brazzini et al. 2003). Inflammation also is a crucial component in cardiovascular diseases, including atherosclerosis. The autonomic nervous system may perform heart-brain communication through cytokine signaling to alter the disease course through anti-inflammatory actions (Shishehbor,

Alves, and Rajagopal, 2007). Neuropsychiatric disorders are influenced by neuroimmune interaction via neurotransmitters and cytokines (Fricchione et al. 2001). Neuroendocrine-immune cross-talk is not limited to inflammation as a triggering factor. Alcohol, for example, may serve as a neurochemical regulator of the HPA axis (Haddad, 2004). Understanding this interaction should facilitate treatment of alcoholic addiction.

In short, research has advanced our understanding of neuroimmune interaction in disease processes over the last decade. This new understanding has introduced a new approach to a variety of disease processes. Both pro-inflammatory cytokines and immune cells have been targeted for the treatment of various diseases. With intensified research, detailed underlying mechanisms will be revealed and innovative strategies will be developed to alter the course of currently debilitating and life threatening diseases.

Acknowledgements

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